Clinical Study Protocol **GE Healthcare**
GE-001-024

Title: A multicentre, phase 3, clinical study to compare the striatal uptake of a dopamine transporter radioligand, DaTSCAN™ ioflupane (^{123}I) injection, after intravenous administration to Chinese patients with a diagnosis of Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, or essential tremor and to healthy controls

REVISED TO INCORPORATE AMENDMENT A03

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Confidentiality Statement

This protocol is provided for conducting a clinical research study. The information contained in this document is confidential and, except to the extent necessary to obtain informed consent or IEC/IRB approval, cannot be disclosed unless required by governmental regulation. Persons to whom any portion of the contents of this document is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Investigators' Signature Page

I have read this protocol and all associated case report forms and agree to conduct this study in full accordance with the stipulations of the protocol described herein.

Signature

Date

Print Name

1 SYNOPSIS

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates **Name of Finished Product:** DaTSCAN™ ioflupane (^{123}I) injection **Name of Active Ingredient:** [^{123}I]Ioflupane	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:** **Volume:** **Reference:**	**(For National Authority Use Only)**

Title of Study: A multicentre, phase 3, clinical study to compare the striatal uptake of a dopamine transporter radioligand, DaTSCAN™ ioflupane (^{123}I) injection, after intravenous administration to Chinese patients with a diagnosis of Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, or essential tremor and to healthy controls

Protocol Number: GE-001-024

Investigators and Study Centres: Approximately 10 centres in the People's Republic of China

Phase of Development: Phase 3

Objectives:

Primary Objective:

- To determine the sensitivity and specificity of a measure of striatal uptake of [^{123}I]ioflupane as visualised in single photon emission computed tomography (SPECT) images taken 3 to 6 hours after a single intravenous (IV) administration of DaTSCAN™ ioflupane (^{123}I) injection (111 to 185 MBq [3 to 5 mCi]) for the diagnosis of Parkinsonian syndrome (PS) involving striatal dopaminergic deficit (SDD; specifically, Parkinson's disease [PD], multiple system atrophy [MSA], or progressive supranuclear palsy [PSP]) as opposed to essential tremor (ET; no SDD) or no neurologic disease (healthy volunteers [HVs]) in Chinese subjects.

Secondary Objectives:

- To assess the striatal uptake of [^{123}I]ioflupane in healthy Chinese volunteers (no SDD).
- To assess safety parameters (haematology, biochemistry and urinalysis, and vital signs) and the adverse event (AE) profile in Chinese patients/HVs after a single IV administration of DaTSCAN™ ioflupane (^{123}I) injection.

Study Design

This is a multicentre, open-label, non-controlled, non-randomised clinical study to compare the SPECT findings after a single IV administration of DaTSCAN™ ioflupane (^{123}I) injection for patients with a clinical diagnosis of PS (SDD; specifically, patients with PD [SDD], MSA [SDD] or PSP [SDD]) as compared with patients with a clinical diagnosis of ET (no SDD) and age-matched healthy controls.

Selection of Subjects:

Inclusion Criteria:

For all subjects:

1. Chinese male or female, aged 40 to 80 years, has agreed to sign and date the written informed consent form.

For HVs:

2. Non-patient volunteers with good age-appropriate health as established by clinical examination during screening and no evidence of movement disorder by complete neurological evaluation.

For patients with PD:

3. A diagnosis of clinically established or clinically probable PD in accordance with the MDS Clinical Diagnostic Criteria for Parkinson's Disease [Postuma et al. 2015].

For patients with MSA (SDD):

4. A diagnosis of probable or possible MSA in accordance with the Second Consensus Statement on the Diagnosis of MSA [Gilman et al. 2008].

For patients with PSP (SDD):

5. A diagnosis of probable or possible PSP in accordance with the Clinical Criteria for the Diagnosis of Progressive Supranuclear Palsy National Institute for Neurological Disorders and Society for PSP (NINDS-SPSP) [Litvan et al. 1996].

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For patients with ET (no SDD)

6. A diagnosis of definite or probable ET in accordance with the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) diagnostic criteria for ET (no SDD) [Louis et al. 1997].

Exclusion Criteria

1. The subject is lactating.
2. The subject is pregnant as detected by a β-human chorionic gonadotropin (β-hCG) pregnancy test.
3. A cerebral structural vascular abnormality indicative of at least 1 infarction in the region of the basal ganglia (including the internal capsule) ≥5 mm has been confirmed, preferably by magnetic resonance imaging (MRI) performed within 6 months of screening. If an MRI is not clinically feasible, cerebral CT imaging within 6 months is also acceptable.
4. The subject is diagnosed with major neurocognitive disorder by the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 criteria, or Mini-Mental State Examination total score is <24.
5. Subject is being investigated for or has been diagnosed and/or is being treated for repeated stroke with stepwise progression of Parkinson features.
6. History of repeated head injury (≥3 concussions, or history of professional sports with repeated head trauma [e.g., boxing]).
7. History of definite encephalitis (≥1 episode of confirmed encephalitis with objective residual neurologic deficit).
8. The subject is using or has insufficient washout from medication known or suspected to interact with striatal uptake through direct competition with binding of DaTSCAN™ to the dopamine transporters (i.e., amphetamine, benztropine, bupropion, cocaine, mazindol, methylphenidate, phentermine, sertraline, selective serotonin reuptake inhibitors) before the imaging visit.
9. The patient is using Chinese traditional medicine for PD treatment, which cannot be safely withdrawn for at least 1 week (7 days) before the imaging visit.
10. The subject has a moderate to severe renal impairment (i.e., serum creatinine >1.5× upper limit of normal [ULN], or blood urea nitrogen [BUN] >30 mg/dL).
11. The subject has a moderate to severe hepatic impairment (bilirubin >2× ULN and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× ULN).
12. The subject has a history of current abuse of drugs and/or alcohol (for the previous 12 months before trial enrolment).
13. The subject has a history of occupational exposure to any radiation >50 mSv/year.
14. The subject has been previously enrolled in this study or participated in a clinical study involving an investigational pharmaceutical product within 30 days prior to screening and/or any radiopharmaceutical within a minimum of 5 radioactive half-lives prior to screening.
15. The subject presents with symptoms suggestive of corticobasal degeneration or Huntington's disease.
16. The subject has known allergies to the investigational medicinal product (IMP).
17. The subject presents with any clinically active, serious, life-threatening disease with a life expectancy of less than 12 months.
18. Any laboratory value(s) exceeding the limits of normality if deemed to be clinically relevant by the investigator.
19. The subject complains of claustrophobia.
20. The subject has a moderate to severe thyroid disease (thyroid stimulating hormone exceeding the limits of normality by more than 10%), if deemed to be clinically relevant by the investigator.

For patients with ET:

21. The patient has at least 1 first-degree relative diagnosed with PD.

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For HVs:
22. History of psychiatric illness.

For all subjects:
23. It is the physician's best judgment not to include the patient in the trial.

Number of Subjects/Centres Planned: It is expected that 150 patients with movement disorders (with and without SDD) and 22 HVs will be needed to provide 140 evaluable subjects (60 with movement disorder and SDD, 60 with movement disorder but without SDD, 20 HVs) at approximately 10 centres in China.

Treatment of Subjects:
Investigational Medicinal Product: DaTSCAN™, a single IV injection containing 111 to 185 MBq (3 to 5 mCi).
Control: None.
Comparator: None.
Standard of Truth: Clinical diagnosis as established at entry (baseline visit) in specialised medical centres.
Adjunctive Drugs: None.
Duration of Treatment: 1 day for injection and scanning and 3 (±1) days post-injection for a final follow-up visit.

Efficacy and Safety Variables
Primary Endpoint:
- Assessment of DaTSCAN™ SPECT images by 3 independent blinded readers to compare specific striatal uptake with the clinical diagnosis.

Secondary Endpoints:
- Central read (by semi-quantitative assessment by use of DaTQUANT™) of DaTSCAN™ SPECT images to compare specific uptake with clinical diagnosis.
- Comparison and assessment of safety parameters and AEs reported by all study participants.

Standard of Truth:
The clinical diagnosis as established by the investigator at the recruiting centres according to internationally accepted diagnostic criteria and based on a standardised and comprehensive clinical and neuropsychiatric assessment will be the standard of truth used for determining sensitivity and specificity.

Safety:
Imaging visit: DaTSCAN™-emergent AEs, injection site monitoring, and vital signs (blood pressure, heart rate).
3 (±1) days post-injection: AEs, physical examination, neurological examination, vital signs (blood pressure and heart rate), clinical laboratory evaluations (haematology, serum biochemistry, and urinalysis), and concomitant medications.

Statistical Methods and Planned Analysis:

Primary Efficacy Analysis:

The sensitivity and specificity of the blinded independent read of DaTSCAN™ SPECT images in detecting or excluding SDD, when the clinical diagnosis as established by the investigator is used as the standard of truth, will be summarised with both by-reader and majority-read analyses. For each summary, the computed value and the 95% 2-sided confidence interval will be presented for both sensitivity and specificity. In this study, sensitivity will be defined as positive percentage agreement, and specificity will be defined as negative percentage agreement. For the specificity analysis, only subjects with a clinical diagnosis of ET will be included; the HVs will be excluded from this analysis. Accuracy will be calculated, and a 2-sided binomial confidence interval constructed around it.

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Secondary Efficacy Analyses:

A semi-quantitative analysis of the striatal uptake ratios in specific regions of interest (ROIs; i.e., left and right striatum, caudate, and putamen) of DaTSCAN™ SPECT images will be performed with DaTQUANT™. To account for nonspecific binding, the DaTSCAN™ uptake in the ROI will be normalised to DaTSCAN™ uptake in the subject's occipital cortex. The normalised DaTSCAN™ uptake values for each ROI will be summarised with descriptive statistics for each category of subjects with SDD (PD, MSA, or PSP) and each category of subjects without SDD (ET and HVs). For all striatal uptake ratios, an analysis of variance (ANOVA) will be carried out to test for differences in the striatal uptake ratios among the clinical diagnosis groups.

Safety Analyses:

All safety data will be listed by subject group, subject number, and time point (if applicable). No inferential testing will be performed for safety parameters.

- An overall summary of AEs and DaTSCAN™-emergent AEs will be presented, coded with Medical Dictionary for Regulatory Activities (MedDRA) and summarised by MedDRA system-organ class and preferred term.
- Observations and changes from baseline in the results of the physical examination (including vital signs), neurological examination, injection site monitoring, and clinical laboratory evaluations (haematology, serum biochemistry, and urinalysis) will be summarised.

Study Populations

The efficacy analysis will be performed for the full analysis set (FAS), which will consist of all subjects who have both a DaTSCAN™ image set and a clinical diagnosis made by the investigator.

The per-protocol (PP) population will include all subjects who meet the inclusion/exclusion criteria and did not withdraw informed consent (if applicable), and who have DaTSCAN™ image sets that are considered evaluable by at least 2 of the 3 blinded readers. Subjects considered for PP population include subjects in the FAS with no major protocol violations. Subjects with protocol violations will be excluded from the PP population but will be included in the FAS.

All subjects who receive an injection of IMP will be included in the safety population.

Sample Size Estimation:

Although the primary efficacy analysis is not inferentially based, sample size calculations are based on hypothesis testing separately for sensitivity and specificity, assuming 1-sided alpha of 0.05, statistical power of 80%, and assumed sensitivity and specificity of 95%.

The null hypothesis tests are given as H_0: $p \leq p_0$ where p_0 is the specified threshold. The alternate hypothesis is given by H_a: $p>p_0$. The parameter p represents the sensitivity/specificity of the blinded independent read of DaTSCAN™ SPECT images in detecting or excluding SDD, using the clinical diagnosis as established by the investigator as the standard of truth.

An exact binomial test with a nominal 0.05 1-sided significance level will have 80% power to detect the difference between the null hypothesis diagnostic sensitivity threshold of 0.85 and the assumed alternative proportion of 0.95 when the sample size is 59 subjects with SDD present.

An exact binomial test with a nominal 0.05 1-sided significance level will have 80% power to detect the difference between the null hypothesis diagnostic specificity threshold of 0.85 and the assumed alternative proportion of 0.95 when the sample size is 59 subjects with SDD absent.

An extensive set of values for the specified threshold, p_0, and the resultant sample size (for either sensitivity or specificity) are as follows: $P_0 = 0.89$: n=128; $P_0 = 0.88$: n=107; $P_0 = 0.87$: n= 89; $P_0 = 0.86$: n= 73; $P_0 = 0.85$: n= 59; $P_0 = 0.84$: n= 55; $P_0 = 0.83$: n= 44; $P_0 = 0.82$: n= 41; $P_0 = 0.81$: n= 39; $P_0 = 0.80$: n=30.

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However, according to regulatory guidelines sample size for a new product with more than 1 indication (which is the case for DaTSCAN) requires a minimum of 60 pairs of cases. Therefore, the final number of evaluable diseased individuals will be 60 in each group (SDD present and absent).
In addition to the 120 evaluable subjects (subjects with movement disorder), each centre will be requested to recruit 2 to 4 HVs (subjects without movement disorder) for the sole purpose of the creation of a normal database. A total of 20 HVs will be recruited across the centres. These subjects will also be included in the safety analysis.
On the basis of a previous study (DP008-003), it is projected that evaluable results will be obtained from 80% of diseased individuals and 90% of HVs. After adjustment for losses, it is therefore expected that 150 patients with movement disorders (with and without SDD) and 22 HVs will be needed to provide at least the minimum required number of evaluable patients.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ATC	Anatomic Therapeutic Chemical
β-hCG	β-human chorionic gonadotropin
BIE	blinded image evaluation
BUN	blood urea nitrogen
CRF	case report form
CRO	contract research organisation
CT	computed tomography
DSM	Diagnostic and Statistical Manual of Mental Disorders
ET	essential tremor
DaT	dopamine transporters
FAS	full analysis set
FDG-PET	[^{18}F]fluorodeoxyglucose positron emission tomography
FN	false negatives
FP	false positives
GCP	Good Clinical Practice
HV	healthy volunteer
H&Y	Hoehn and Yahr
IB	investigator brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IV	intravenous
IRB	Institutional/Independent Review Board
MDS-UPDRS	Movement Disorder Society United Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
MSA	multiple system atrophy
MSA-C	multiple system atrophy with predominant cerebellar ataxia
MSA-P	multiple system atrophy with predominant parkinsonism
NINDS-SPSP	National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy
PD	Parkinson's disease
PP	per-protocol
PSP	progressive supranuclear palsy
SAE	serious adverse event
SDD	striatal dopaminergic deficit
SmPC	summary of product characteristics
SOPs	standard operating procedures
SPECT	single photon emission computed tomography
TN	true negatives
TP	true positives

ULN	upper limit of normal
UPDRS	United Parkinson's Disease Rating Scale
WHIGET	Washington Heights-Inwood Genetic Study of Essential Tremor

4 BACKGROUND INFORMATION

Parkinson's disease (PD) is a slowly progressing neurodegenerative disease with a variable prevalence in the People's Republic of China. Since 1985, many PD prevalence studies have been conducted in China, covering 9 provinces [Li et al. 2019]. Based on published data, the average prevalence of PD in China was approximately 3.8756% (≥50 years old) in the Han population, 1.234% in Uygur ethnicity, 1.208% in Kazak, and 1.224% in Hui ethnicity, respectively [Liu et al. 2010] [Jianlong et al. 2013] [Yang et al. 2015] [Li et al. 2019]. Regarding incidence of PD in China, 1 study, which was performed in IIan country of Taiwan, showed the incidence was 10.4 per 100,000 with a slightly higher rate in men compared to women (11.1 per 100,000 vs. 9.8 per 100,000 in women) [Chen et al. 2001].

The prevalence of PD increases with age. A recent multicentre, cross-sectional study using a stratified cluster sampling approach showed that the prevalence in Chinese veterans is comparable to that in other countries and regions and suggested a gradual increase tendency in the oldest old population. The estimated number of cases of PD in China was 1.72 to 1.99 million in 2005. The number is projected to increase to 4.95 million (approximately half of the global disease burden) in 2030 [Zhou et al. 2014].

The diagnosis of PD is based mostly on clinical symptoms and a favourable response to levodopa therapy. However, patients manifest symptoms only when 50% to 80% of the nigrostriatal neurons are lost. Clinical methods cannot provide an early diagnosis before a significant loss of dopamine neurons has occurred. Additionally, some authors have indicated that almost 25% of patients with an ante-mortem clinical diagnosis may not have PD in clinical-pathological studies [Wu et al. 2014]. It is therefore clear that new tests that can improve/or accelerate diagnosis of PD are needed to assist with the clinical assessment.

The hallmark of this disease is a slow, progressive degeneration of the nigrostriatal dopaminergic system, which can be visualised in vivo by using various probes (i.e., radiotracers that can bind to different receptors in the dopaminergic system) [Wang et al. 2012].

DaTSCAN™ is an intravenously administered single-dose radiopharmaceutical that allows single photon emission computed tomography (SPECT) imaging of dopamine transporters (DaT) in the striata of the brain. The information provided by DaTSCAN™ SPECT images may assist in the diagnostic assessment of subjects with suspected movement disorders such as Parkinsonian syndromes (PS) involving striatal dopaminergic deficit (SDD). These disorders encompass PD, multiple system atrophy (MSA), and progressive supranuclear palsy (PSP). In contrast, essential tremor (ET) does not involve SDD [DaTSCAN™ Product Information].

DaTSCAN™ ioflupane (^{123}I) injection has been extensively studied in Europe and the United States for diagnostic imaging in suspected cases of PD [O'Brien et al. 2014]. The information derived from a DaTSCAN™ SPECT image has prognostic value and can be used to guide treatment decisions [Bajaj et al. 2013]. [redacted]

5 STUDY OBJECTIVES AND PURPOSE

Primary Objective

- To determine the sensitivity and specificity of a measure of striatal uptake of [^{123}I]ioflupane as visualised in SPECT images taken 3 to 6 hours after a single intravenous (IV) administration of DaTSCAN™ ioflupane (^{123}I) injection (111 to 185 MBq [3 to 5 mCi]) for the diagnosis of PS involving SDD (specifically, PD, MSA, or PSP) as opposed to ET (no SDD) or no neurologic disease (healthy volunteers [HVs]) in Chinese subjects.

Secondary Objectives

- To assess the striatal uptake of [^{123}I]ioflupane in healthy Chinese volunteers (no SDD).

- To assess safety parameters (haematology, biochemistry and urinalysis, and vital signs) and the adverse event (AE) profile in Chinese patients/HVs after a single IV administration of DaTSCAN™ ioflupane (^{123}I) injection.

6 STUDY DESIGN

6.1 Overall Study Design and Plan

This is a multicentre, open-label, non-controlled, non-randomised clinical study to compare the SPECT findings after a single IV administration of DaTSCAN™ ioflupane (^{123}I) injection for patients with a clinical diagnosis of PS (SDD; specifically, patients with PD [SDD], MSA [SDD] or PSP [SDD]) as compared with patients with a clinical diagnosis of ET (no SDD) and age-matched healthy controls.

This study will be conducted at approximately 10 centres in China. The planned sample size for this clinical investigation will be 140 evaluable subjects (60 with movement disorder and SDD, 60 with movement disorder but without SDD, 20 HVs). On the basis of a previous study (DP008-003), it is projected that evaluable results will be obtained from 80% of diseased individuals and 90% of HVs. After adjustment for losses, it is therefore expected that 150 patients with movement disorders (with and without SDD) and 22 HVs will be needed to provide the minimum required number of evaluable patients.

Each subject will be required to visit the study centre for a screening visit, baseline visit, DaTSCAN™ imaging visit, and 1 follow-up visit. In order to prevent misinterpretations of the DaTSCAN™ SPECT images by the independent blinded readers (who will not be supplied with clinical data), the absence of structural abnormalities in the basal ganglia must be ruled out by a magnetic resonance imaging (MRI) scan performed within 6 months prior to inclusion. If an MRI scan is not clinically feasible, cerebral computed tomography (CT) image findings will also be accepted. If the subject does not have an MRI scan, one will be offered (provided no contraindications are met). If an MRI is not feasible, the investigator will consider offering a CT scan.

During the baseline visit, safety assessments and an extensive neurologic examination will be performed. At that visit, each subject will receive a clinical diagnosis (e.g., PD or ET or no neurologic disease).

The dose of DaTSCAN™ to be used in this study is within the range of 111 to 185 MBq (3 to 5 mCi) per subject in a maximum volume of 5 mL (see Sections 6.2.2 and 8.3). The selected dose is within the range used in previous phase 3 studies and in current clinical practice in Europe and the United States. To minimise thyroid uptake of radioactive iodine, subjects should undergo appropriate thyroid blocking treatment prior to and/or after injection according to local practices.

During the DaTSCAN™ imaging visit, all subjects will receive a single IV injection of DaTSCAN™ ioflupane (^{123}I) injection. SPECT imaging will be performed between 3 to 6 hours post-injection and will last approximately 20 minutes to 1 hour, depending on type of SPECT camera. The DaTSCAN™ imaging visit may occur as soon as possible after the baseline visit but no later than 28 days after baseline. Each subject will be asked to return for a final follow-up visit at 3 (±1) days after the administration of DaTSCAN™ ioflupane (^{123}I) injection.

Subjects will receive the investigational medicinal product (IMP) under direct supervision of hospital personnel. Each administration dose in MBq will be checked, and the vial code, dose, volume per administration will be recorded in each subject's case report form (CRF).

Safety will be assessed from the rates of AEs, changes in vital signs, changes in physical examination findings, changes in clinical laboratory findings, changes in injection site monitoring, and changes in neurologic examination.

Subjects will return to the study centre for a follow-up visit at 3 (±1) days after DaTSCAN™ injection for a safety assessment. To rule out any metabolic disturbances that may underlie changes in neuropsychiatric state, routine laboratory parameters, including glucose and those reflecting hepatic and renal function, will also be assessed.

For further details, refer to Table 1 (Study Schedule of Events) and Figure 1 (Study Flow Chart).

Figure 1 Study Flow Chart

Within 28 days before imaging visit

Screening Visit
- Informed consent
- Assign subject number
- Inclusion/exclusion criteria
- Demographic information
- Medical and surgical history
- Neuropsychiatric history (including dementia history)
- Safety assessments (vital signs)
- Neurological examination
- Neuropsychiatric examination (Section 9.1)
- Prior and concomitant medications
- Pregnancy test (serum ß-hCG test for women of child-bearing potential)
- Laboratory tests (Section 9.1)
- Adverse events

⇓

Within 28 days before imaging visit

Baseline Visit
- Concomitant medication
- Adverse events
- Physical examination
- Neurological examination
- Neuropsychiatric examination
- Investigator's clinical diagnosis
- Eligibility check

⇓

Imaging Visit
- Concomitant medication
- Pregnancy test (hCG urine test; if appropriate)
- Final eligibility check
- Administer thyroid blocking drug (see Section 8.1.4) according to local practice
- Safety assessments (vital signs; pre- and post-injection)
- Injection site monitoring (pre- and post-injection)
- DaTSCAN™ injection
- SPECT Imaging (must be performed within 3 to 6 hours after injection)
- Adverse events

⇓

3 (±1) days after injection

Follow-up Visit
- Concomitant medications
- Laboratory tests (haematology, serum biochemistry, and urinalysis)
- Safety assessments (vital signs)
- Neurological examination
- Physical examination
- Adverse events

6.2 Study Rationale

6.2.1 Justification for the efficacy analysis of diagnosis of PS

PD is characterised by the progressive degeneration of the dopamine-producing neurons in the substantia nigra pars compacta, and the ventral tegmental area [Gibb and Lees 1991], [Bernheimer et al. 1973]. As a result of this neuronal loss, a marked decrease of striatal dopamine content can be detected [Hornykiewicz and Kish 1986]. The dopaminergic nigrostriatal neuron bundle is crucial in the function of the neostriatum (caudate nucleus and putamen) and its control of movement. MSA and PSP also involve progressive degeneration of dopaminergic nigrostriatal neurons that may produce a DaTSCAN™ image that is indistinguishable from that of a patient with PD. In contrast, the dopaminergic nigrostriatal bundle is not involved in the aetiology of ET. Nevertheless, patients with ET have often been given a misdiagnosis of PD [Guberman 1994].

The reliability of the clinical diagnosis of PD is approximately 76% [Hughes et al. 1993], [Meara et al. 1999]. Clinical studies have shown that visual assessment of DaTSCAN™ SPECT images permits detection of loss of functional dopaminergic nigrostriatal neurons and confirm that DaTSCAN™ imaging can discriminate PS from ET. However, it cannot differentiate the different PS subtypes: PD, MS, and PSP.

Longitudinal studies have shown an average age-related decline in DAT availability of 5.5 % per decade both sexes [Varrone et al. 2013], justifying the addition of a group of age-matched controls who will be expected to show some decline in the uptake of DaTSCAN™ with no movement disorders.

6.2.2 Justification for dose and volume

Pilot and pivotal clinical studies have demonstrated that visual assessment of DaTSCAN™ SPECT images permits detection of any nigrostriatal disorder and confirms that DaTSCAN™ can discriminate Parkinson's symptoms from ET. [redacted] The results of several studies have validated the efficacy of DaTSCAN™ within the currently approved dose range and in accordance with the Summary of Product Characteristics (SmPC) and Package Insert.

DaTSCAN™ with extended shelf-life (370 MBq [10 mCi] in 5 mL at reference time) will be supplied to allow administration of radioactivity within the required dose range of 111 to 185 MBq (3 to 5 mCi).

6.2.3 Justification for prohibited and permitted medication

Agents with high affinity for DAT, such as amphetamine, benztropine, bupropion, cocaine, mazindol, methylphenidate, phentermine, sertraline, and selective serotonin reuptake inhibitors, are identified as having interaction potential with DaTSCAN™ and are, therefore, prohibited in the study. Additionally, it is uncertain how traditional Chinese medicines

prescribed to treat PD may affect the DAT. Therefore, if the medication cannot be safely withdrawn at least 1 week before DaTSCAN™ SPECT is performed these patients will also be excluded.

Drugs shown during clinical trials not to interfere with DaTSCAN™ imaging include amantadine, benzhexol, budipine, levodopa, metoprolol, primidone, propranolol, and selegiline. Dopamine agonists and antagonists acting on the postsynaptic dopamine receptors are not expected to interfere with DaTSCAN™ imaging and can therefore be continued if desired. Drugs shown in animal studies not to interfere with DaTSCAN™ imaging include pergolide.

6.2.4 Justification of safety plan

This study's safety monitoring plan is justifiable and adequate from a safety standpoint in view of the following:

- The design of the safety plan permits an appropriate and adequate evaluation of the safety response to DaTSCAN™ under baseline and post-study drug injection conditions in the same subject.
- The design of the safety plan allows a comparison of this study's safety data set with other phase 3 studies.
- The measures used to assess safety are well defined and reliable within the context of the SPECT imaging environment, and the proposed safety analyses are adequate to assess the effects of DaTSCAN™.
- The safety plan aims to restrict the collection of data up to and including 4 days, based on the pharmacokinetic characteristics of DaTSCAN™ and the absence of any study procedures beyond the follow-up visit taking place at 3 (±1) days post administration.

6.3 Study Timeframe

The recruitment period will be approximately 18 months, with an approximate 1 month of study participation per subject. The overall study duration is approximately 18 months from First Patient First Visit to Last Patient Last Visit.

6.4 Risks and Benefits to Subjects

The SPECT images that will be produced in this study can provide diagnostic information that could help to differentiate PS from ET. Thus, subjects with a movement disorder could benefit if the results of the study are used to guide treatment decisions. The HVs are not expected to have a direct benefit.

DaTSCAN™ is a radiopharmaceutical and as such involves exposure to ionising radiation. The maximal effective dose (i.e., the one corresponding to an injection of 185 MBq) is 4.35 mSv for a 70 kg individual, which represents approximately twice the annual average dose to inhabitants in China [Pan et al. 1994] and falls within the limits of other commonly performed diagnostic tests in nuclear medicine and radiology [Health Physics Society].

No serious AEs (SAEs) related to DaTSCAN™ administration have been reported. Commonly reported AEs (not believed to be related to DaTSCAN™) are headache, nausea, dizziness, nasopharyngitis, vertigo, increased appetite, and formication. Intense pain on injection has been reported uncommonly following administration into small veins.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Procedures for Enrolment

Subjects will be recruited by means accepted by the respective regulatory bodies/local health authority (in accordance with local regulations) and the local independent ethics committee (IEC).

The study population will consist of subjects with a clinical diagnosis of PS, subjects with a clinical diagnosis of ET, and HVs. The subjects will be recruited from movement disorder clinics and general neurology clinics.

Each potential subject will attend the centre for a screening visit. Only the individuals who fulfil all of the inclusion criteria (Section 7.2) and none of the exclusion criteria (Section 7.3) will be recruited for the study. Written, dated, and witnessed informed consent will be obtained from all subjects or their legally acceptable representatives prior to study entry and prior to any protocol-specific procedures.

Sufficient subjects will be recruited to obtain the required number of evaluable subjects. The distribution will be assessed on an ongoing basis during the trial using an Interactive Web Response System. Subjects will be assigned a unique identification number during the screening visit, after the informed consent document has been signed and dated.

7.2 Inclusion Criteria

For all subjects:

1. Chinese male or female, aged 40 to 80 years, has agreed to sign and date the written informed consent form.

For HVs:

2. Non-patient volunteers with good age-appropriate health as established by clinical examination during screening and no evidence of movement disorder by complete neurological evaluation.

For patients with PD:

3. A diagnosis of clinically established or clinically probable PD in accordance with the MDS Clinical Diagnostic Criteria for Parkinson's Disease [Postuma et al. 2015], Appendix 15.1.1.

For patients with MSA (SDD):

4. A diagnosis of probable or possible MSA in accordance with the Second Consensus Statement on the Diagnosis of MSA [Gilman et al. 2008], Appendix 15.1.2.

For patients with PSP (SDD):

5. A diagnosis of probable or possible PSP in accordance with the Clinical Criteria for the Diagnosis of Progressive Supranuclear Palsy National Institute for Neurological Disorders and Society for PSP (NINDS-SPSP) [Litvan et al. 1996], Appendix 15.1.3.

For patients with ET (no SDD)

6. A diagnosis of definite or probable ET in accordance with the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) diagnostic criteria for ET (no SDD) [Louis et al. 1997], Appendix 15.1.4.

7.3 Exclusion Criteria

1. The subject is lactating.

2. The subject is pregnant as detected by a β-human chorionic gonadotropin (β-hCG) pregnancy test.

3. A cerebral structural vascular abnormality indicative of at least 1 infarction in the region of the basal ganglia (including the internal capsule) ≥5 mm has been confirmed, preferably by MRI performed within 6 months of screening. If an MRI is not clinically feasible, cerebral CT imaging within 6 months is also acceptable.

4. The subject is diagnosed with major neurocognitive disorder by the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 criteria, or Mini-Mental State Examination total score is <24.

5. Subject is being investigated for or has been diagnosed and/or is being treated for repeated stroke with stepwise progression of Parkinson features.

6. History of repeated head injury (≥3 concussions, or history or professional sports with repeated head trauma [e.g., boxing]).

7. History of definite encephalitis (≥1 episode of confirmed encephalitis with objective residual neurologic deficit).

8. The subject is using or has insufficient washout from medication known or suspected to interact with striatal uptake through direct competition with binding of DaTSCAN™ to the DaT (i.e., amphetamine, benztropine, bupropion, cocaine, mazindol, methylphenidate, phentermine, sertraline, selective serotonin reuptake inhibitors) before the imaging visit.

9. The patient is using Chinese traditional medicine for PD treatment, which cannot be safely withdrawn for at least 1 week (7 days) before the imaging visit.

10. The subject has a moderate to severe renal impairment (i.e., serum creatinine >1.5× upper limit normal [ULN], or blood urea nitrogen [BUN] >30 mg/dL).

11. The subject has a moderate to severe hepatic impairment (bilirubin >2× ULN and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× ULN).

12. The subject has a history of current abuse of drugs and/or alcohol (for the previous 12 months before trial enrolment).

13. The subject has a history of occupational exposure to any radiation >50 mSv/year.

14. The subject has been previously enrolled in this study or participated in a clinical study involving an investigational pharmaceutical product within 30 days prior to screening and/or any radiopharmaceutical within a minimum of 5 radioactive half-lives prior to screening.

15. The subject presents with symptoms suggestive of corticobasal degeneration or Huntington's disease.

16. The subject has known allergies to the IMP.

17. The subject presents with any clinically active, serious, life-threatening disease with a life expectancy of less than 12 months.

18. Any laboratory value(s) exceeding the limits of normality if deemed to be clinically relevant by the investigator.

19. The subject complains of claustrophobia.

20. The subject has a moderate to severe thyroid disease (thyroid stimulating hormone exceeding the limits of normality by more than 10%), if deemed to be clinically relevant by the investigator.

For patients with ET:

21. The patient has at least 1 first-degree relative diagnosed with PD.

For HVs:

22. History of psychiatric illness.

For all subjects:

23. It is the physician's best judgement not to include the patient in the trial.

7.4 Withdrawal and Termination Criteria

7.4.1 Subject withdrawal

There are no formal withdrawal criteria for this study. During the conduct of the study, the sponsor will review the safety data for trends and signals that would indicate the need for withdrawal of a subject.

In accordance with the Declaration of Helsinki, each subject is free to withdraw from the study at any time. Investigator(s) also have the right to withdraw subjects from the study in the event of illness, AEs, or other reasons concerning the health or well-being of the subject, or in the case of lack of co-operation.

Should a subject decide to withdraw after administration of the IMP(s), or should the investigator(s) decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for withdrawal must be noted in the CRF. If the reason for withdrawal is a clinical AE, monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded in the CRF.

7.4.2 Study or site termination

Both the sponsor and principal investigator reserve the right to terminate the study at the respective centre at any time. Before terminating the study, the sponsor and investigator will ensure that a careful review of the overall risk/benefit analysis confirms the balance to be no longer acceptable. Should termination be necessary, both parties will arrange the procedures after review and agreement with the IEC. In terminating the study, the sponsor and investigator will assure that adequate consideration is given to the protection of all the subjects having been recruited.

Study enrolment will be stopped when the planned number of evaluable subjects has been enrolled. The sponsor or the health authorities may terminate an investigator centre if serious protocol violations occur.

8 TREATMENT OF SUBJECTS

8.1 Description of Medicinal Products

8.1.1 Investigational medicinal product: DaTSCAN™ ioflupane (^{123}I) injection

In this study, each subject will receive 1 dose of the IMP in this study, DaTSCAN™ ioflupane (^{123}I) injection, during the imaging visit. Each patient will receive a dose of 111 to 185 MBq in a maximum volume of 5 mL. To minimise pain upon injection, the dose will be delivered by a slow IV injection (not less than 15 to 20 seconds) into an arm vein.

DaTSCAN™ ioflupane (^{123}I) injection is a sterile, pyrogen-free radiopharmaceutical for IV injection. The clear and colourless solution is supplied in single-use vials in which each millilitre contains 0.07 to 0.13 µg ioflupane, 74 MBq (2 mCi) of iodine 123 (as ioflupane [^{123}I]) at calibration time, 5.7 mg acetic acid, 7.8 mg sodium acetate, and 0.05 mL (5%) ethanol. The pH of the solution is between 4.2 and 5.2.

Iodine 123 is a cyclotron-produced radionuclide that decays to tellurium 123 by electron capture and has a physical half-life of 13.2 hours. The principal radiation emitted by ^{123}I is γ radiation (159 keV).

Only personnel authorised by Chinese regulations to handle radioactive materials will be allowed to handle DaTSCAN™.

DaTSCAN™ (Ioflupane (^{123}I) Injection) preparations will not be used after the expiration date and time stated on the label.

Appropriate radiation precautions should be observed during the preparation and storage of the agent. Aseptic technique with sterile syringes and needles should be used.

8.1.2 IMP accountability

Each investigator is responsible for ensuring that deliveries of IMP(s) and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with all applicable regulatory guidelines, and used in accordance with this protocol.

All IMP containers (opened, unopened, or empty) must be destroyed on site after the study and overall drug accountability have been completed by the representative. A list of IMP(s) and other materials that were destroyed, must be prepared and signed by the principal investigator or designee. If there are any discrepancies, an explanation for these should also be provided.

Any package inserts, SmPCs, or other safety documents for IMPs or adjunctive study materials will be supplied to the site.

8.1.3 Registration of investigational medicinal product(s) complaints

In the event of an IMP complaint (e.g., breakage, leakage, particulate matter, discoloration), the investigator or recipient of the IMP is requested to report the problem on the IMP shipping documentation (e.g., 'Delivery Note for Product', Drug Shipping and Receiving Form, or equivalent form). This documentation should be promptly forwarded to the person indicated on the shipping documentation. Once the complaint is received, the Clinical Supplies Manager will register the complaint and determine, according to sponsor procedures, if the complaint is minor or significant. All complaints will be followed up, and the appropriate action will be implemented according to sponsor procedures.

8.1.4 Other medicinal products: Thyroid-blocking treatment

To minimise thyroid uptake of radioactive iodine, subjects must undergo appropriate thyroid blocking treatment prior to and/or after injection according to local practice. The thyroid blocking agent will be preferably sourced locally by the hospital. If it is not available in the hospital, then sponsor should source it. The administered time, date and dose will be captured on the concomitant medication page.

8.2 Method of Numbering Subjects and Assigning Subjects to Treatment Groups

In this open-label study, all subjects will undergo the same procedure: diagnostic imaging with DaTSCAN™ ioflupane (^{123}I) injection.

Each subject will be given a unique identification number. The identification number will be assigned to the subject during the screening visit, after the informed consent document has been signed and dated. Once an identification number has been assigned, it cannot be reassigned, even if the subject is deemed ineligible or withdraws consent. No subject may enter the study more than once. Nor may a subject be re-screened for the study after having failed to meet the inclusion/exclusion criteria. If the investigator has any question about any subject's eligibility to participate in the study, the investigator or study personnel should contact the sponsor to discuss the subject's eligibility.

Each subject's identification number will consist of a 3-digit site code plus a 4-digit consecutive number. For example, site "999" will assign the number "999-0001" to its first subject, "999-0002" to its second subject, and so on. To preserve the integrity of the study, it is crucial that these numbers be assigned in consecutive numerical order.

All subjects will receive the same treatment. Therefore, there will be no assignment to treatment groups.

No randomisation will take place in this study. For analysis, the subjects will be assigned to diagnostic categories according to their clinical diagnosis (e.g., PD, MSA, PSP, ET, or HV).

8.3 Selection of Doses and Timing

The dose of DaTSCAN™ ioflupane (^{123}I) injection to be used in this study is based on the dose that has been approved by the regulatory authorities in Europe and in the United States.

The dose of this radiopharmaceutical is calculated in terms of radioactivity. Clinical efficacy has been demonstrated across the range 111 to 185 MBq. The dose should not exceed 185 MBq, and the product should not be used when the activity is below 111 MBq. Because of the short half-life of ^{123}I, the dose to be administered to the subject is calculated in relation to the reference time on the label.

DaTSCAN™ is a 5% (v/v) ethanolic solution for IV injection and should be used without dilution. To minimise the potential for pain at the injection site during administration, a slow IV injection (not less than 15 to 20 seconds) via an arm vein is recommended.

SPECT imaging should take place between 3 and 6 hours after the administration of DaTSCAN™ ioflupane (^{123}I) injection.

8.4 Blinding

This is an open label study where all individuals will receive a dose of DaTSCAN™ and no blinding of the IMP will be performed.

A blinded image evaluation (BIE) will be performed as described in Section 10.2.3.

8.5 Prior and Concurrent Therapy

If a subject is taking a prohibited medication that **cannot** be withdrawn, the subject must be excluded from participation in the study. If during the pre-treatment and treatment phases of the study the use of any prohibited medication becomes necessary for medical reasons, the subject will be withdrawn from further participation in the study.

The investigator should avoid the concomitant administration of any medication that is known or suspected of negative interaction with DaTSCAN™. The minimum washout period for all generally prohibited concomitant medications is 5 half-lives prior to imaging. If the patient is using Chinese traditional medicine for PD treatment, the minimum washout period required to enter the study is 1 week (7 days).

The following list of prohibited concomitant medications does not represent a complete list, and as such should only be used as a guide for the investigator: psychostimulants (e.g., amphetamine), benztropine, bupropion, cocaine, mazindol, methylphenidate, phentermine, sertraline. Selective serotonin reuptake inhibitors (paroxetine and citalopram) may increase or decrease ioflupane binding to the DaT. Updated information on concomitant therapy, if any, will be provided in the DaTSCAN™ investigator brochure (IB).

Before one of the above-prohibited medications is withdrawn from a subject to satisfy inclusion/exclusion criteria, the investigator will seek the subject's agreement on the informed consent form as well as the agreement of the referring physician and document it in the subject's medical notes. The investigator will then implement and oversee an appropriate drug-withdrawal regimen.

8.5.1 Permitted concomitant medications

Clinical trials have shown that the following drugs do not interfere with DaTSCAN™ imaging: amantadine, benzhexol, budipine, levodopa, metoprolol, primidone, propranolol, and selegiline. Dopamine agonists and antagonists acting on the postsynaptic dopamine receptors are not expected to interfere with DaTSCAN™ imaging and can therefore be continued if desired. In preclinical studies, pergolide did not interfere with DaTSCAN™ imaging.

The sponsor will encode all therapy and medication according to a World Health Organization preferred term dictionary of medical codes (see Section 12.4.1).

8.6 Treatment Compliance

The IMP will be administered by study personnel. Each administration volume and the total radioactivity injected will be checked and the vial code, dose, volume per administration will be recorded in each subject's CRF. Doses administered outside of specific dose requirements or defined range must be reported as protocol deviations (see Section 13.3).

9 STUDY PROCEDURES

All efficacy and safety measurements obtained during the course of the study are summarised in the Study Schedule of Events (Table 1).

Table 1 Study Schedule of Events

	Screening Visit [a]	Treatment						
		Baseline Visit [a]	Imaging Visit					Follow-up
			Pre-injection			Post-injection		
	Within 28 days prior to imaging visit	Within 28 days prior to imaging visit	Within 1 to 4 hours prior to injection	Within 30 min prior to injection	0	10 min	3 to 6 hours	3 (±1) days [b]
Informed consent	X							
Subject number assignment	X							
Demographic information	X							
Inclusion/exclusion criteria	X	X	X					
Medical and surgical history	X							
Neuropsychiatric history (including dementia history)	X							
Neurological examination	X	X						X
Pregnancy test (if applicable)	X		X					
Prior and concomitant medication	X----------							----------X
Laboratory tests [c]	X							X
Physical examination		X						X
Neuropsychiatric examination (Section 9.1) [d]	X	X						
Clinical diagnosis		X						
Vital signs (blood pressure, heart rate)	X			X			X	X
Thyroid blocking			X[e]				X[e]	
Injection site monitoring				X	X	X	X	
DaTSCAN™ injection					X			
SPECT imaging							X[f]	
Adverse events	X----------							----------X

[a] The screening visit and baseline visit may be combined and conducted on the same day.
[b] Performed at 3 (±1) days after injection of DaTSCAN™
[c] Some tests will only be performed at screening (refer to Section 10.3.3, Table 2)
[d] Mini Mental State Examination, UPDRS-III, United Parkinson's Disease Rating Scale Part III; H&Y, Hoehn and Yahr and WHIGET assessment
[e] The dosage and timing of administration will be based on investigator's discretion according to local practice of each site (e.g., to be administered within 1 to 4 hours prior to and 12 to 24 hours after injection of DaTSCAN™ are just for reference)
[f] Performed 3 to 6 hours after injection of DaTSCAN™

9.1 Screening Visit

At the screening visit (within 28 days prior to the imaging visit), the following will be performed/recorded:

- Signed and dated informed consent
- Assign subject number
- Inclusion criteria and exclusion criteria (listed in Sections 7.2 and 7.3)
- Demographic information
- Medical and surgical history
- Neuropsychiatric history (including dementia history)
- Neurological examination
- Neuropsychiatric examination:
  - Mini-Mental State Examination
  - United Parkinson's Disease Rating Scale (UPDRS) Part III assessment
  - Hoehn and Yahr Scale for PD
  - WHIGET assessment for ET
- Vital signs (blood pressure, heart rate)
- Pregnancy test (serum ß-hCG test; if applicable)
- Prior and concomitant medications
- Blood and urine samples for laboratory testing (see Table 2).
- AEs

The screening visit and baseline visit may be combined and conducted on the same day. All procedures for both visits have to be completed at this combined visit. Laboratory results for the subject must be available and assessed by investigators before the imaging visit is scheduled.

9.2 Baseline Visit

At the baseline visit (within 28 days prior to the imaging visit) the following will be performed/recorded:

- Physical examination
- Neurological examination
- Neuropsychiatric examination
- Concomitant medication
- Investigator's clinical diagnosis
- Eligibility check
- AEs

9.3 Imaging Visit

The imaging visit will take place as soon as possible but within 28 days after the baseline visit (Table 1).

The following will be performed 1 to 4 hours before administration of IMP:

- Concomitant medication
- Pregnancy test (hCG urine test; if applicable)
- Final eligibility check
- Administer thyroid blocking drug (see Section 8.1.4) according to local practice
- AEs

Within 30 minutes prior to the injection of IMP, the following will be performed/recorded:

- Vital signs
- Injection site examination
- AEs

The subject will then receive a dose of IMP as described in Sections 8.1 and 8.3.

Post-IMP injection, the following will be performed/recorded:

- Injection site examination: 10 minutes and 3 to 6 hours post-IMP injection
- Imaging: 3 to 6 hours post-IMP injection(see Section 10.2 and the Imaging Manual)
- Vital signs: 3 to 6 hours post-IMP injection
- AEs
- Administer thyroid blocking drug (see Section 8.1.4) according to local practice

9.4 Follow-up Visit (3 [±1] days after injection)

At the follow-up visit scheduled for 2 to 4 days after injection, the following will be performed/recorded (Table 1):

- Neurological examination
- Concomitant medications
- Clinical laboratory tests
- Physical examination
- Vital signs
- AEs

9.5 Unscheduled Visits

An unscheduled visit can be arranged at the discretion of the investigator. At a minimum, the date and reason for the visit will be captured. Any procedures performed will also be captured in the CRF.

10 EFFICACY, SAFETY, AND OTHER VARIABLES

10.1 Efficacy Assessments

10.1.1 Primary endpoint

- Assessment of DaTSCAN™ SPECT images by 3 independent blinded readers to compare specific striatal uptake with the clinical diagnosis.

10.1.2 Secondary endpoints

- Central read (by semi-quantitative assessment by use of DaTQUANT™) of DaTSCAN™ SPECT images to compare specific uptake with clinical diagnosis.
- Comparison and assessment of safety parameters and AEs reported by all study participants.

10.2 Technical Requirements for DaTSCAN™ SPECT Image Acquisition

10.2.1 Image acquisition

Images will be acquired within the pre-specified time window and without any interference in appropriate medical care; the latter will take priority. Acquired image data will be anonymised and all Personal Health Information will be removed at site before electronic transmission to the Sponsor for the BIE. The sponsor will prepare and distribute an Imaging Manual that describes all image acquisition and transmittal procedures.

Prior to the first DaTSCAN™ image acquisition, equipment will be checked to ensure compliance with the requirements for DaTSCAN™ image acquisition and data transfer. Details of SPECT hardware qualification requirements are presented in the Imaging Manual.

10.2.2 Standard of truth

The clinical diagnosis as established by the investigator at baseline at the recruiting centres according to internationally accepted diagnostic criteria and based on a standardised and comprehensive clinical and neuropsychiatric assessment will be the standard of truth used for determining sensitivity and specificity.

10.2.3 Image interpretation and correlation with standard of truth

Anonymised DaTSCAN™ SPECT images will be presented in randomized order to 3 independent readers. Each blinded image reviewer will determine if the image is of sufficient quality to be interpretable. If the image is not interpretable, the blinded image reviewer will be required to specify the reason why on the CRF. If the image is considered evaluable by the reader, then the reader will be required to record his/her assessment of the subject's image in terms of a normal pattern of tracer uptake (negative image interpretation) or an abnormal pattern of tracer uptake (positive image interpretation). If the image is classified as abnormal, he/she will be asked to further classify the image as typical SDD or atypical SDD.

The BIE readers will evaluate the DaTSCAN™ SPECT images according to the following classification:

1. Normal DaTSCAN™ SPECT images: 2 symmetric comma- or crescent-shaped focal regions of activity mirrored about the median plane. Striatal activity is distinct, relative to surrounding brain tissue
2. Abnormal DaTSCAN™ SPECT image type 1: Activity is asymmetric (i.e., activity in the region of the putamen of 1 hemisphere is absent or greatly reduced with respect to the other). Activity is still visible in the caudate nuclei of both hemispheres, resulting in a comma or crescent shape in 1 and a circular or oval focus in the other. There may be reduced activity between ≥1 striatum and surrounding tissues
3. Abnormal DaTSCAN™ SPECT image type 2: Activity is absent in the putamen of both hemispheres and confined to the caudate nuclei. Activity is relatively symmetric and forms 2 roughly circular or oval foci. Activity of one or both is generally reduced.
4. Abnormal DaTSCAN™ SPECT image type 3: Activity is absent in the putamen of both hemispheres and greatly reduced in one or both caudate nuclei. Activity of the striata with respect to the background is reduced.
5. Other: Abnormal pattern, not conforming to any of the patterns above, to be specified by the reviewer (e.g., 'punched-out' lesion such as caused by an ischaemic stroke) or if the image cannot be interpreted.

Where an image cannot be assigned to one of the categories 1) to 5) a reason must be specified in the CRF.

The readers will be blinded to subject Personal Health Information, details of the originating institution, and all other clinical information except for the subject's age. Because of an overall decrease in cerebral circulatory capacity with increasing age, the specific nigrostriatal DaTSCAN™ uptake decreases and the non-specific uptake increases. Thus, knowledge of the subject's age is required for appropriate evaluation of the SPECT images.

The BIE will be conducted in accordance with the study Independent Review Charter prepared by the sponsor.

10.3 Safety Assessments

The following safety data will be collected and evaluated, as detailed in Table 1:

- Physical examination
- Neurological examination
- Vital signs: blood pressure, heart rate
- Laboratory tests for haematology, serum biochemistry (including vitamin B_{12}, folic acid, thyroid function, and C-reactive protein), tests for syphilis, and urinalysis (refer to Table 2)
- AEs
- Injection site monitoring

10.3.1 Physical examinations

A physical examination will be conducted at baseline and at a follow-up visit at 3 (±1) days post-injection (see Table 1).

A licensed physician will conduct the physical examinations. If possible, the same physician should conduct the physical exam at both time points.

A physical examination will include an assessment for the presence of abnormalities in:

- General appearance
- Lungs
- Cardiovascular system
- Abdomen

A neurological examination will include an assessment for the presence of abnormalities of the following:

- Level of consciousness
- Cranial nerves (II-XII)
- Motor function
- Sensory function
- Proprioception/position sense of extremities
- Reflexes (biceps, triceps, patellar, ankle)
- Mood and affect
- Cognitive function

- Cerebellar
- Speech
- Orientation
- Memory
- Gait

In the event that “new” or “worsening” abnormal physical examination findings are encountered during the study, these terms are defined as follows:

- A “new” abnormal physical examination finding is defined as one that occurs when a subject's normal baseline physical examination becomes abnormal post-baseline, based on clinical grounds.

- A “worsening” abnormal physical examination finding is defined as one that occurs when a subject's abnormal baseline physical examination becomes worse post-baseline, also based on clinical grounds.

New and worsening abnormal physical examination findings qualify as AEs.

10.3.2 Vital signs

Vital signs variables will include measurements of systolic and diastolic blood pressure and heart rate. Blood pressure and heart rate measurements will be obtained at screening, within 30 minutes prior to injection, within 3 to 6 hours and at 3 (±1) days post-injection (see Table 1).

All blood pressure measurements will be taken on the arm contralateral to the site of DaTSCAN™ injection. Before vital signs are measured, the subject should be resting for at least 5 minutes. The same position will be used each time vital signs are measured for a given subject.

10.3.3 Clinical laboratory evaluation

10.3.3.1 Measurements

Laboratory measurements to be assessed in this study are displayed in Table 2.

Table 2 Laboratory Measurements

Serum Biochemistry	**Haematology**	**Urinalysis (Dipstick)**
Creatinine	Haematocrit	Bilirubin
Urea nitrogen	Haemoglobin	Protein
Bilirubin (total)	Red blood cell (RBC) count	Urobilinogen
Albumin	White blood cell (WBC) count	Glucose
Aspartate aminotransferase	WBC Differential	Ketone
Alanine aminotransferase	Platelet count	Occult blood
Alkaline phosphatase		Specific gravity
γ-Glutamyl transferase		Leukocytes
Sodium	**Tests for**	pH
Potassium	Syphilis (at screening only)	
Lactate dehydrogenase		
Creatine phosphokinase		
Vitamin B_{12} (at screening only)		
Folic acid (at screening only)		
Calcium		
Phosphate		
Glucose		
Thyroid function (at screening only)		
C-reactive protein (at screening only)		

Laboratory measurements will be examined for clinically notable values according to central laboratory reference ranges and clinically notable criteria.

The signed and interpreted laboratory results will be kept together with the subject's CRF as supplemental pages, both centrally and at the site.

10.3.3.2 Blood sampling

Clinical laboratory tests to be evaluated in this study include haematology, serum biochemistry (including vitamin B_{12}, folic acid, thyroid function, and C-reactive protein), and tests for syphilis. Tests for vitamin B_{12}, folic acid, thyroid function, C-reactive protein, and syphilis are to be performed only at screening. Blood samples will be collected at screening (within 28 days prior to injection) and at the follow-up visit at 3 (±1) days post-injection. All samples will be analysed at a central laboratory.

10.3.3.3 Urinalysis

Urinalysis will be performed at screening (within 28 days prior to injection) and at 3 (±1) days post-injection (Follow-up Visit). The time of void will be documented on the CRF. Midstream urine will be collected. Urine voided will be tested at the investigator site using urinary dipstick. Any patients with positive protein and/or blood in urinalysis at screening will be

further investigated for urinary tract infection and adequately treated by the investigator prior to study entry.

10.3.4 Injection site monitoring

The injection site will be evaluated for physical evidence of local/regional adverse outcomes at the following time points: within 30 minutes prior to injection, during injection, at 10 minutes post-injection, and 3 to 6 hours post-injection (see Table 1). The abnormal injection site findings include, but are not limited to, radiopharmaceutical extravasation, bleeding, haematoma, redness, and infection.

Any abnormal finding that is new or represents a worsening from baseline is an AE.

10.3.5 Adverse events

All AEs/SAEs that occur after informed consent shall be recorded in the AE/SAE report form (see the Study Schedule of Events, Table 1).

Study personnel must remain vigilant for the occurrence of AEs after administration of IMP, particularly those that may be life threatening. Personnel who are trained in the acute management of anaphylaxis and other emergencies and who have access to appropriate clinical supplies must be immediately available for 1 hour after dosing. Treatment of SAEs should be primarily supportive of vital functions.

AE and DaTSCAN™-emergent AE definition: An AE is defined as any untoward medical occurrence or an already present event that worsens either in intensity or frequency. A DaTSCAN™-emergent AE is defined as an AE that starts on or after the time of the injection of DaTSCAN™ until the follow-up visit at 3 (±1) days later. The DaTSCAN™-emergent AE does not necessarily have to have a causal relationship with exposure to the investigational agent. A DaTSCAN™-emergent AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the exposure to the IMP, whether or not considered related to that product.

The subjects will be closely observed and questioned for any kind of AE during the study procedures and throughout the study period with non-leading questioning (e.g., “How do you feel?”). The subjects will be instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations).

If an AE has already been reported it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if myocardial infarction is reported as an AE, there is no need to report an elevated creatine phosphokinase, abnormal ECG, or other related signs, symptoms, or laboratory values as separate AEs.

All AEs/SAEs and all DaTSCAN™-emergent AEs/SAEs shall be collected up to the time point of finalisation of the last safety examination during the follow-up performed at 3 (±1) days post-injection.

Causal relationship

Both the investigator(s) and Sponsor/contract research organisation (CRO) will perform a causality assessment on any AE, to assess whether or not there is a reasonable possibility (evidence to suggest) that the IMP caused the event.

The relationship of an AE with DaTSCAN™ will be assessed and reported by the investigator as:

- Reasonably related to study drug ("Reasonable cause"): - A causal relationship between DaTSCAN™ and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- Not reasonably related to study drug ("Not reasonable cause"): - A causal relationship between DaTSCAN™ and an AE is not a reasonable possibility.

Suspected Adverse Reaction: A suspected adverse reaction is an AE where reasonable possibility exists for causality between DaTSCAN™ and the AE.

Expectedness

All DaTSCAN™-emergent AEs will be assessed, by the sponsor (or CRO on behalf of sponsor), as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the applicable safety information included in the reference safety information in the IB for DaTSCAN™.

Unexpected: An unexpected DaTSCAN™-emergent AE is a reaction, for which the nature, seriousness, severity or outcome is not consistent with the applicable safety information included in the IB.

Expected: An expected DaTSCAN™-emergent AE is a reaction which is consistent with the applicable safety information included in the IB.

10.3.5.1 Serious adverse events

An SAE is defined as any AE that:

- Results in death.
- Is immediately life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is another important medical event.*

*Other important medical events are those that may not result in death, be life-threatening, or require hospitalisation, but may be considered a SAE when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical intervention to prevent 1 of the outcomes listed in this definition.

10.3.6 Other significant adverse events

Clinically notable results from vital signs, clinical laboratory, and injection site findings should be reported as AEs, where applicable.

10.3.7 Adverse event and serious adverse event reporting

All AEs shall be recorded in the AE/SAE report form using acceptable diagnoses, if possible. If an AE has already been reported (by the investigator to the sponsor/CRO) it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if myocardial infarction is reported as an AE, there is no need to report elevated creatine kinase and abnormal ECG, or other related signs, symptoms, or laboratory values as separate AEs. However, if both occurred in isolation and myocardial infarction was not diagnosed, then each event would be reported as an AE.

The intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:

Mild:	Tolerable.
Moderate:	Interferes with normal activity.
Severe:	Incapacitating (causes inability to perform usual activity or work). The investigator will be instructed to closely monitor each patient who experiences an AE (whether ascribed to DaTSCAN™ or not) until the outcome of the AE has been determined.

In addition to the investigator's own description of the AEs, each AE will be encoded by the sponsor/CRO according to a well-recognised dictionary of medical codes (Medical Dictionary for Regulatory Activities [MedDRA]).

All serious and non-serious AEs must be followed for a final outcome until the end of the follow-up period. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for non-serious AEs at the end of a patient's participation in a study, and for SAEs at database lock.

Study centres are instructed to report all SAEs (including DaTSCAN™-emergent SAEs), together with a causality assessment, to the sponsor (or a service provider/CRO acting on behalf of the sponsor) within 24 hours. The Sponsor will review SAEs as they are received, and report to Health Authority as per local regulation.

All AEs and SAEs are reported in the AE form of the CRF. Detailed information about management of AE information will be provided, e.g., in a Safety Management Plan or equivalent document.

10.3.8 Urgent safety measures

In accordance with the principles of Good Clinical Practice (GCP) as laid out in International Conference on Harmonisation (ICH) E6, the investigator(s) has/have primary responsibility for assuring subject safety throughout the performance of study procedures. An urgent safety measure is defined as any measure which an investigator may need to implement which is a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior favourable opinion from the IEC or institutional review board (IRB).

The investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazards to their health or safety. However, the investigator must inform the sponsor/CRO within 24 hours of having taken such measures.

The sponsor in turn shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the licensing authority and the relevant IEC/IRB of the measures taken and the circumstances giving rise to those measures.

All urgent safety measures must be reported to the sponsor/CRO using the SAE contact numbers provided in a separate document (as stipulated in in Section 10.3.7) within 24 hours of having to take such a measure(s). Such reports can be initiated by telephone but must be officially documented by the investigator (by email or fax) and must include details of what measures were taken and the circumstances giving rise to those measures.

10.3.8.1 Pregnancy reporting

This process is aimed at ensuring the appropriate monitoring of the potential risk related to IMP exposure of pregnant women and/or foetuses as well as the risks associated with exposure of a father, regarding congenital abnormalities or birth defects in their offspring. It also ensures compliance with applicable international and local regulations.

The requirements are applicable to all subjects following exposure to IMP.

Female trial subjects: The study patient must be advised by the investigator to inform him/her immediately if she suspects she may be pregnant and believes conception occurred within 72 hours of DaTSCAN™ administration

Male trial subjects: The study patient must be advised by the investigator to inform him/her immediately if he suspects his partner became pregnant within 72 hours after DaTSCAN™ administration.

When a trial subject reports a pregnancy (post-IMP administration) to the investigator, a pregnancy test should be arranged for the trial subject (or their partner) by the investigator within 7 days of the pregnancy being reported.

The investigator must inform the sponsor/CRO within 24 hours of receiving positive pregnancy test results using either a copy of the relevant CRF page (demography or AE) or via e-mail. The investigator should include an estimated date of conception when communicating with the sponsor/CRO.

10.4 Other Variables

10.4.1 Demographic data

The following demographic data will be collected at the screening visit

- Age
- Gender
- Weight
- Height
- Race
- Level of education

10.4.2 Medical and surgical history

The medical and surgical history will be recorded at the baseline visit.

10.4.3 Prior and concomitant medication

The subjects will be asked about prior and concomitant medications at the screening visit (within 28 days prior to the screening visit), at the baseline (from screening visit to baseline visit), at the imaging visit (from baseline visit to imaging visit), and at the follow-up visit (from imaging visit to follow-up visit). History of treatment response to medications used to treat PD, MSA, PSP and ET will be recorded. At the imaging visit, the investigator will review the list of medications to determine whether sufficient washout from any prohibited medication and from traditional Chinese medication has been achieved to determine final eligibility.

At the baseline visit, the date and time of the last dose of PD treatments prior to UPDRS Part III will be recorded as part of UPDRS Part III.

10.4.4 Drug and alcohol screening

At the screening visit, subjects will be asked about a history of drug or alcohol abuse.

10.4.5 Neuropsychiatric assessments

At the screening and baseline visit, the following assessments will be performed:

- Mini-Mental State Examination (MMSE): The MMSE is a simplified, cognitive mental status examination focusing on the cognitive aspect of mental function. It is an examiner-led evaluation and consists of 11 questions [Folstein et al. 1975].

- Movement Disorder Society United Parkinson's Disease Rating Scale (MDS-UPDRS) Part III assessment: MDS-UPDRS Part III [Goetz et al. 2008] will be used to assess any presence of motor symptoms of parkinsonism. Examiners should complete online training for the MDS-UPDRS Part III examination. Results will be captured in the CRF.

- Modified Hoehn and Yahr (H&Y) Scale for Parkinson's Disease: The 8-point Modified H&Y scale will be used.

- WHIGET assessment for ET: The WHIGET Tremor Rating Scale (version 1) was developed for the purpose of identifying patients with ET in population studies. This version, published in 1997 [Louis et al. 1997], has inclusion and exclusion criteria for distinguishing ET from other forms of action tremor. It is a 10-minute tremor examination designed to elicit rest tremor, rest tremor and kinetic tremor. Postural and kinetic tremors elicited from a battery of tasks are rated from 0 to 3 [Elble et al. 2013].

Results of these assessments, together with medical and medication history will be used to determine the clinical diagnosis at the baseline visit.

10.4.6 Investigator's clinical diagnosis

The investigator will establish clinical diagnosis of the subject at the baseline visit. Diagnosis will be made by using the following internationally accepted diagnostic criteria:

- MDS Clinical Diagnostic Criteria for Parkinson's Disease
- Second Consensus Statement on the Diagnosis of MSA
- Clinical Criteria for the Diagnosis of Progressive Supranuclear Palsy National Institute for Neurological Disorders and Society for PSP
- WHIGET diagnostic criteria for ET (no SDD)

All available data at the site will be used to establish the diagnosis, including medical records, comprehensive medical history, clinical examination, neuropsychiatric assessment and laboratory results collected at screening and baseline visit.

10.5 Appropriateness of Measurements

All assessments and measurements are appropriate and generally regarded as standard medical practice.

11 DATA HANDLING AND QUALITY ASSURANCE

11.1 Completing and Signing Case Report Forms

For electronic CRFs, data will be entered by trained site personnel. Any errors should be corrected within the electronic system. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error. The appropriate electronic signature will be provided.

11.2 Clinical Data Management

The sponsor or CRO will be responsible for the processing and quality control of the data. Data management will be carried out by the CRO. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

11.3 Archiving

All study documentation at the investigator site and sponsor site will be archived in accordance with ICH E6-GCP and the GE Healthcare's quality standards and standard operating procedures (SOPs).

All study documentation at the Investigator site and sponsor site will be archived as required by local regulatory legislation following completion or discontinuation of the study, unless notified otherwise by the sponsor. The Investigator must request written agreement from the sponsor before destruction of archived study documentation.

12 STATISTICAL METHODS AND PLANNED ANALYSIS

The data will be analysed by the sponsor and/or designated CRO. Any data analysis carried out independently by the investigator should be submitted to the sponsor before publication or presentation.

Data from participating centres in this protocol will be combined so that an adequate number of subjects will be available for analysis. The data will be summarised with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements.

12.1 General Statistical Considerations

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed with SAS® software, Version 9.2 or higher. Descriptive statistics for continuous data in summary tables will include the number of subjects in the analysis (n), mean, standard deviation, median, and range (minimum, maximum). Descriptive statistics for categorical data in summary tables will include counts and percentages. The last observation prior to administration of IMP will be used as the baseline value for calculating changes from baseline after administration of IMP. All data recorded on the CRF and entered into the database will be provided in separate data listings showing individual subject values. All summary tables and data listings will be separated by baseline diagnosis. The planning and reporting of statistical analysis will be carried out as described in the sponsor and/or CRO's SOPs governing clinical studies.

12.2 Populations for Analysis

12.2.1 Full analysis set (FAS)

The efficacy analysis will be performed for the full analysis set (FAS), which will consist of all subjects who have both a DaTSCAN™ image set and a clinical diagnosis made by the investigator.

12.2.2 Per-protocol (PP) population

The per-protocol (PP) population will include all subjects who meet the inclusion/exclusion criteria and did not withdraw informed consent (if applicable), and who have DaTSCAN™ image sets that are considered evaluable by at least 2 of the 3 blinded readers. Subjects considered for PP population include subjects in the FAS with no major protocol violations.

Subjects with protocol violations will be excluded from the PP population but will be included in the FAS. Subjects with protocol violations will be identified in the study report.

12.2.3 Safety population

All subjects who receive an injection of IMP will be included in the safety population.

12.3 Subject Demographics/Other Baseline Characteristics

12.3.1 Subject disposition

A table will be provided with the following information:

- Number of subjects enrolled.
- Number of subjects included in the efficacy analysis.
- Number of subjects included in the safety analysis.
- Number of subjects withdrawn from the study and the reason for withdrawal.

12.3.2 Demographic data

Demographic information (age, height, weight, and body mass index) will be summarised by using descriptive statistics. Sex and race will be summarised by counts and percentages.

12.3.3 Risk factors and medical history

Pregnancy information, medical/surgical history, and history of any disease classification will be summarised by counts and percentages.

12.3.4 Clinical diagnosis

The clinical diagnosis of PS (SDD; specifically, PD, MSA, or PSP) or no SDD (ET or healthy controls) as determined by the investigator at entry will be summarised by counts and percentages.

12.4 Study Treatments

12.4.1 Previous and concurrent medication

Any prior and concurrent therapy or medication (and the indication for the treatment) given to a subject from 28 days prior to IMP administration and throughout the follow-up period after IMP administration will be tabulated by counts and percentages. The World Health Organization Drug Global Dictionary, Version September 1, 2018 or later, using Anatomic Therapeutic Chemical (ATC) and Herbal ATC Code Level 3, and preferred name will be used.

12.4.2 Exposure to IMP

The following information will be recorded and summarised with descriptive statistics:

- The radioactivity (in megabecquerels) of the syringe before injection.
- The volume (in millilitres) of IMP administered.
- The total radioactivity administered.
- The duration of injection.
- The saline flush volume.

12.4.3 Thyroid blockade

The amount and type of medication used for thyroid blockade for each subject will be summarised.

12.4.4 Handling of uninterpretable images as determined by the BIE

Subjects with image(s) that cannot be interpreted from the BIE will be excluded from the primary analysis but will be included to determine the sensitivity of results.

12.4.5 Handling of uninterpretable images

Uninterpretable images will be excluded from the efficacy analysis. All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate. The number and proportion of images that are uninterpretable will be displayed in tables.

12.4.6 Reader difference

Intra-reader (within-reader) agreement of blinded visual image assessment will be measured by percentage agreement. This will be based on a random selection of 10% of the subjects having re-read images. A percentage agreement with an exact 95% confidence interval will be determined for each reader comparison and all readers for subjects with re-reads of images.

In cases where images are re-read, it is the result of the first read that is to be included in the efficacy analysis.

12.5 Efficacy Analysis

Efficacy analyses will be performed on both the FAS and PP populations defined in Section 12.3.

12.5.1 Primary efficacy analysis

The sensitivity and specificity of the blinded independent read of DaTSCAN™ SPECT images in detecting or excluding SDD, when the clinical diagnosis as established by the investigator is used as the standard of truth, will be summarised with both by-reader and majority-read analyses. For each summary, the computed value and the 95% 2-sided binomial confidence interval will be presented for both sensitivity and specificity.

12.5.1.1 Sensitivity

In this study, sensitivity will be defined as positive percentage agreement. Sensitivity will be calculated as the number of true positives (TP) / (number of TP + number of false negatives [FN]): TP/(TP + FN), and a 2-sided 95% binomial confidence interval constructed around it.

12.5.1.2 Specificity

In this study, specificity will be defined as negative percentage agreement. Specificity will be calculated as the number of true negatives (TN) / (number of TN + number of false positives [FP]): TN/(TN + FP), and a 2-sided 95% binomial confidence interval constructed around it. For the specificity analysis, only subjects with a clinical diagnosis of ET will be included; the HVs will be excluded from this analysis.

12.5.1.3 Accuracy

Accuracy will be calculated as (TP + TN) / (TP + FN + TN + FP), and a 2-sided 95% binomial confidence interval constructed around it.

12.5.2 Secondary efficacy analyses

12.5.2.1 Semi-quantitative analysis

A semi-quantitative analysis of the striatal uptake ratios in specific regions of interest (ROIs; i.e., left and right striatum, caudate, and putamen) of DaTSCAN™ SPECT images will be performed with DaTQUANT™. To account for nonspecific binding, the DaTSCAN™ uptake in the ROI will be normalised to DaTSCAN™ uptake in the subject's occipital cortex. The normalised DaTSCAN™ uptake values for each ROI will be summarised with descriptive statistics for each category of subjects with SDD (PD, MSA, or PSP) and each category of subjects without SDD (ET and HVs). For all striatal uptake ratios, an analysis of variance (ANOVA) will be carried out to test for differences in the striatal uptake ratios among the clinical diagnosis groups.

12.6 Safety Analyses

12.6.1 Safety variables and analyses

All safety data will be listed by subject group, subject number, and time point (if applicable). No inferential testing will be performed for safety parameters.

- An overall summary of AEs and DaTSCAN™-emergent AEs will be presented, coded with MedDRA and summarised by MedDRA system organ class and preferred term.

- Observations and changes from baseline in the results of the physical examination (including vital signs), neurologic examination, injection site monitoring, and clinical laboratory evaluation (haematology, serum biochemistry, and urinalysis) will be summarised (see Table 1).

12.6.1.1 Clinical laboratory evaluation

Descriptive statistics will be displayed for the observed values and changes from baseline. In addition, for each clinical laboratory variable and each time point, the following safety endpoints will be summarised by counts and percentages for the overall safety population and for each diagnostic group subset:

- The occurrence of 1 or more changes from baseline, at each post-administration time point, greater than 40% and 80% of the span of the normal limits (not applicable to qualitative parameters).

- The occurrence of post-administration values outside the normal limits (not applicable to qualitative parameters). Shift tables based on the normal range will be prepared.

12.6.1.2 Vital signs

Descriptive statistics will be displayed for the observed values and changes from baseline. For each vital-sign variable and each time point, the following safety endpoints will be summarised by counts and percentages for the overall safety population and for each subject group:

- The occurrence of 1 or more changes from baseline, at each post-administration time point, greater than a pre-specified magnitude (20 mm Hg for systolic blood pressure, 10 mm Hg for diastolic blood pressure, 10 beats per minute for heart rate).

- The occurrence of post-administration values outside the normal limits. Shift tables based on the normal range will be prepared.

12.6.1.3 Physical examination

Baseline findings and the number and percentage of subjects with changes in physical examination status from normal at baseline to abnormal at each post-administration time point

(and vice versa) will be presented for the safety population and for each subject group. Shift tables based on normal vs abnormal results will be prepared.

12.6.1.4 Neurological examination

Baseline findings and the number and percentage of subjects with changes in neurological examination status from normal at baseline to abnormal at each post-administration time point (and vice versa) will be presented for the safety population and for each subject group. Shift tables based on normal vs abnormal results will be prepared.

12.6.1.5 Injection site monitoring

Injection site findings will be summarised by time point for the safety population and for each subject group.

12.6.1.6 Adverse events

An overall summary of AEs and DaTSCAN™-emergent AEs will be presented, coded with MedDRA and summarised by MedDRA system organ class and preferred term for the safety population and for each subject group. Summaries will also be presented by AE intensity and judged relationship to IMP.

SAEs will be separately presented for the safety population and for each subject group.

Other significant AEs, defined as laboratory abnormalities that qualify as AEs (other than those meeting the definition for serious) and any events that led to an intervention (including premature discontinuation of IMP, dose reduction, or significant additional concomitant therapy), in addition to those reported as SAEs, will be summarised for the safety population and for each subject group.

12.7 Sample Size Calculation

Although the primary efficacy analysis is not inferentially based, sample size calculations are based on hypothesis testing separately for sensitivity and specificity, assuming 1-sided alpha of 0.05, statistical power of 80%, and assumed sensitivity and specificity of 95%.

The null hypothesis tests are given as H_0: $p \leq p_0$ where p_0 is the specified threshold. The alternate hypothesis is given by H_a: $p>p_0$. The parameter p represents the sensitivity/specificity of the blinded independent read of DaTSCAN™ SPECT images in detecting or excluding SDD, using the clinical diagnosis as established by the investigator as the standard of truth.

An exact binomial test with a nominal 0.05 1-sided significance level will have 80% power to detect the difference between the null hypothesis diagnostic sensitivity threshold of 0.85 and the assumed alternative proportion of 0.95 when the sample size is 59 subjects with SDD present.

An exact binomial test with a nominal 0.05 1-sided significance level will have 80% power to detect the difference between the null hypothesis diagnostic specificity threshold of 0.85 and the assumed alternative proportion of 0.95 when the sample size is 59 subjects with SDD absent.

An extensive set of values for the specified threshold, p_0, and the resultant sample size (for either sensitivity or specificity) are as follows: $P_0 = 0.89$: n=128; $P_0 = 0.88$: n=107; $P_0 = 0.87$: n= 89; $P_0 = 0.86$: n= 73; $P_0 = 0.85$: n= 59; $P_0 = 0.84$: n= 55; $P_0 = 0.83$: n= 44; $P_0 = 0.82$: n= 41; $P_0 = 0.81$: n= 39; $P_0 = 0.80$: n=30.

However, according to regulatory guidelines sample size for a new product with more than 1 indication (which is the case for DaTSCAN™) requires a minimum of 60 pairs of cases. Therefore, the final number of evaluable diseased individuals will be 60 in each group (SDD present and absent).

In addition to the 120 evaluable subjects (subjects with movement disorder), each centre will be requested to recruit 2 to 4 HVs (subjects without movement disorder) for the sole purpose of the creation of a normal database. A total of 20 HVs will be recruited across the centres. These subjects will also be included in the safety analysis.

On the basis of a previous study (DP008-003), it is projected that evaluable results will be obtained for 80% of diseased individuals and 90% of HVs. After adjustment for losses, it is therefore expected that 150 patients with movement disorders (with or without SDD) and 22 HVs will be needed to provide at least the minimum required number of evaluable subjects.

12.8 Power for Analysis of Critical Secondary Variables

No power analysis was performed on any of the secondary variables.

12.9 Procedures for Missing, Unused and Spurious Data

Missing values will not be substituted by estimated values but treated as missing in the statistical evaluation. All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

12.10 Rules for Excluding Subjects from Analysis

All dosed subjects will be included in the analyses unless otherwise specified. The sponsor will make any decisions regarding whether any subjects or any individual values belonging to a subject will be excluded from the statistical evaluation (tables, plots, and analyses). Apart from the conditions on excluding subjects from the efficacy population stated in Section 12.2, subjects will only be excluded from the evaluations when a protocol violation is considered to imperil the scientific aspects and interpretation of the study results. If the subject has received any IMP, all available safety data will be used. The reason(s) for any exclusion will be described in the report.

12.11 Procedures for Reporting Deviations from Original Statistical Plan

Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the final Clinical Study Report.

13 SPECIAL REQUIREMENTS AND PROCEDURES

13.1 Regulatory, Institutional and Ethical Review

Before this study is started, the protocol (authorized by the sponsor) will be submitted to the regulatory bodies/local health authorities (in accordance with local regulations) and to the IEC/IRB for evaluation. The protocol will also be signed by the principal investigator before submission to the IEC/IRB. The study will not start before the IEC/IRB gives written approval or a favourable opinion in accordance with ICH E6-GCP and all applicable regulatory bodies/local health authorities give approval or a favourable opinion as required.

No changes from the final approved (authorized) protocol will be initiated without the IEC's/IRB's prior written approval or favourable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The sponsor will authorize and the principal investigator(s) will sign the protocol amendment prior to submission to the IEC/IRB. Protocol amendments should be submitted to the IEC/IRB without delay.

13.2 Investigator's Responsibilities

13.2.1 Overall responsibilities

The investigator(s) is/are responsible for conducting the study in full accordance with the Protocol and the Declaration of Helsinki, the *Good Clinical Practice: Consolidated Guideline*, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any investigational centres participating in this study that cannot comply with these standards will be documented.

13.2.2 Subject informed consent

Written and oral information about the study in a language understandable by the subject and/or their legally acceptable representative will be given to all subjects and/or their legally acceptable representatives. Each subject's willingness to participate in the study will be documented in a signed and dated informed consent form before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the subjects and/or their legally acceptable representatives that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The informed consent process will be documented in the subject's medical record and the investigator will sign, date the informed consent form after the subject and/or their legally acceptable representative has signed and dated the document. The investigator(s) will keep the original consent forms and copies will be given to the subjects and/or their legally acceptable representatives.

13.2.3 Direct access to source data/documents

The monitor(s), auditor(s), authorized personnel of the sponsor/CRO, health authority inspector(s) or their agents, and authorized members of IECs/IRBs will be given direct access to source data and documentation (e.g., medical charts/records, laboratory results, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

13.2.4 Confidentiality regarding study subjects

The investigator(s) must assure that the privacy of the subjects, including their personal identity and all other personal medical information, will be maintained at all times. In CRFs and other documents or image material (including materials from all examinations, e.g., MRI, SPECT examinations) submitted to the sponsor/CRO, subjects will not be identified by their names, but by an identification code (e.g., study subject number).

Personal medical information may be scrutinized for the purpose of verifying data recorded in the CRF. This may be done by the monitor(s), properly authorized persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

13.3 Protocol Deviations

Any deviation from the protocol when no approved amendment exists must be documented as a protocol deviation and reported according to local requirements. If appropriate, corrective and preventative action must be implemented to avoid repetition. Protocol deviations and any potential impact on the study results will be discussed during the reporting of the study.

Waivers or protocol exceptions will not be granted prospectively by the sponsor under any circumstances. Any exceptions to protocol specified requirements will be considered as protocol deviations.

13.4 Study Monitoring

Study monitoring will be performed in accordance with ICH E6-GCP, the Sponsor/CRO SOPs, the protocol, and applicable local regulations.

13.5 Audit and Inspection

According to ICH E6-GCP, the sponsor or regulatory authorities may audit the investigational site. The sponsor’s Quality Assurance Unit, independent of the Clinical Research and Development Department, is responsible for auditing the study.

The investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

13.6 Radioactive Licence Requirements

The investigators must have the appropriate license (Nuclear Regulatory Commission By-product Material Site License) for any procedure involving the administration of radioactive substances supplied by the sponsor. If radiolabelled materials will be shipped from the sponsor to the study site, a copy of the clinical site's Nuclear Regulatory Commission license must be provided to the sponsor and archived in the Trial Master File before the radiolabelled material can be shipped.

13.7 Insurance

This study is covered under the sponsor's Liability Insurance Policy (under General Electric Insurance Company and/or a company designated by the study Sponsor). A Certificate of Insurance and/or an information leaflet containing essential information about the insurance coverage can be provided upon request.

13.8 Publication Policy

The investigator and/or Institution shall have the right to publish the results of their work conducted under this protocol, subject to providing the sponsor with the opportunity to review the contents of any proposed abstract or publication concerning the work, including any results of the study, in advance of publication and if necessary to delay publication for a limited time not to exceed 60 days in order to protect the confidentiality or proprietary nature of any information contained therein. The sponsor will make every reasonable effort to consider and release each proposed publication within 30 days, or proposed abstract within 15 days, of submission.

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15 APPENDICES

15.1 Clinical Diagnostic Criteria

15.1.1 MDS Clinical Diagnostic Criteria for Parkinson's Disease [Postuma et al. 2015]

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS-Unified Parkinson Disease Rating Scale. Once parkinsonism has been diagnosed:

Diagnosis of Clinically Established PD requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of Clinically Probable PD requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   If 1 red flag is present, there must also be at least 1 supportive criterion
   If 2 red flags, at least 2 supportive criteria are needed
   No more than 2 red flags are allowed for this category

Supportive criteria
(Check box if criteria met)

☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response, a dramatic response can be classified as:
   a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
   b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

☐ 2. Presence of levodopa-induced dyskinesia

☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)

☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute exclusion criteria: The presence of any of these features rules out PD:

☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)

☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades

☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria31 within the first 5 y of disease

☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y

☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism

☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease

☐ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system
☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than PD

Red flags
☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
☐ 3. Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
a) Orthostatic hypotension32—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination

Criteria Application:
1. Does the patient have parkinsonism, as defined by the MDS criteria? Yes ☐ No ☐
If no, neither probable PD nor clinically established PD can be diagnosed. If yes:
2. Are any absolute exclusion criteria present? Yes ☐ No ☐
If "yes," neither probable PD nor clinically established PD can be diagnosed. If no:
3. Number of red flags present ____
4. Number of supportive criteria present ____
5. Are there at least 2 supportive criteria and no red flags? Yes ☐ No ☐
If yes, patient meets criteria for clinically established PD. If no:
6. Are there more than 2 red flags? Yes ☐ No ☐
If "yes," probable PD cannot be diagnosed. If no:
7. Is the number of red flags equal to, or less than, the number of supportive criteria? Yes ☐ No ☐
If yes, patient meets criteria for probable PD

15.1.2 Second Consensus Statement on the Diagnosis of Multiple System Atrophy [Gilman et al. 2008]

Criteria for the diagnosis of probable MSA

- A sporadic, progressive, adult (>30 year)-onset disease characterized by
- Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 minutes of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic and
- Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction).

Criteria for possible MSA

- A sporadic, progressive, adult (>30 year)-onset disease characterized by
- Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) and
- At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency, or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) and
- At least one of the additional features of possible MSA.

Additional features of possible MSA

Possible MSA with predominant parkinsonism (MSA-P) or with predominant cerebellar ataxia (MSA-C)

- Babinski sign with hyperreflexia.
- Stridor.

Possible MSA-P

- Rapidly progressive parkinsonism.
- Poor response to levodopa.
- Postural instability within 3 years of motor onset.
- Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction.
- Dysphagia within 5 years of motor onset.

- Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum.
- Hypometabolism on [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) in putamen, brainstem, or cerebellum.

Possible MSA-C

- Parkinsonism (bradykinesia and rigidity).
- Atrophy on MRI of putamen, middle cerebellar peduncle, or pons.
- Hypometabolism on FDG-PET in putamen.
- Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET.

Features supporting (red flags) and not supporting a diagnosis of MSA

Supporting features

- Orofacial dystonia.
- Disproportionate antecollis.
- Camptocormia (severe anterior flexion of the spine) and/or Pisa syndrome (severe lateral flexion of the spine).
- Contractures of hands or feet.
- Inspiratory sighs.
- Severe dysphonia.
- Severe dysarthria.
- New or increased snoring.
- Cold hands and feet.
- Pathologic laughter or crying.
- Jerky, myoclonic postural/action tremor.

Non-supporting features

- Classic pill-rolling rest tremor.
- Clinically significant neuropathy.
- Hallucinations not induced by drugs.
- Onset after age 75 years.
- Family history of ataxia or parkinsonism.
- Dementia (on DSM-IV).
- White matter lesions suggesting multiple sclerosis.

15.1.3 Clinical Criteria for the Diagnosis of Progressive Supranuclear Palsy National Institute for Neurological Disorders and Society for PSP (NINDS-SPSP) [Litvan et al. 1996]

Mandatory Inclusion Criteria

PSP Possible

- Gradually progressive disorder.
- Onset at age 40 years or later.
- Either vertical (upward or downward gaze) supranuclear palsy[a] or both slowing of vertical saccades and prominent postural instability with tendency to fall[b] in the first year of disease onset.
- No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria.

PSP Probable

- Gradually progressive disorder.
- Onset at age 40 years or later.
- Vertical (upward or downward gaze) supranuclear palsy[a] and prominent postural instability with tendency to fall[b] in the first year of disease onset.
- No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria.

Definite PSP[c]

- Clinically probable or possible PSP and histopathologic evidence of typical PSP

Mandatory exclusion criteria

- Recent history of encephalitis
- Alien limb syndrome, cortical sensory deficits, focal frontal or temporoparietal atrophy
- Hallucinations or delusions unrelated to dopaminergic therapy.
- Cortical dementia of Alzheimer's type (severe amnesia and aphasia or agnosia, according to NINCDS-ADRDA criteria).
- Prominent, early cerebellar symptoms or prominent, early unexplained dysautonomia (marked hypotension and urinary disturbances).
- Severe asymmetric parkinsonian signs (i.e., bradykinesia).
- Neuroradiologic evidence of relevant structural abnormality (i.e., basal ganglia or brainstem infarcts, lobar atrophy).

- Whipple's disease, confirmed by polymerase chain reaction, if indicated.

Supportive criteria

- Symmetric akinesia or rigidity, proximal more than distal.
- Abnormal neck posture, especially retrocollis.
- Poor or absent response of parkinsonism to levodopa therapy.
- Early dysphagia and dysarthria.
- Early onset of cognitive impairment including at least 2 of the following: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behaviour, or frontal release signs.

[a]Upward gaze is considered abnormal when pursuit or voluntary gaze, or both, have a restriction of at least 50% of the normal range.

[b]Tendency to fall is not the same as actual falls, as some patients have caregivers who accompany or catch them, and patients may also be more cautious (I. Litvan, personal communication, July 25, 2012).

[c]Definite PSP is a clinicopathologic diagnosis.

15.1.4 Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) diagnostic criteria for ET (no SDD) [Louis et al. 1997]

Protocol for Tremor Examination

While subject is seated:

(1) Hands resting in lap for 15 seconds

(2) Arms held at 90º for 15 seconds (arm sustension)

(3) Arms held in wing position for 15 seconds

(4) Pouring water from one cup to another (cups should be standard size and at least three quarters filled; 8 transfers)

(5) Bringing a spoon of water from lap level up to mouth and back again; repeat 7 additional times

(6) Drinking water from a full glass; repeat 7 times with each hand

(7) Finger-nose-finger on right 8 times

(8) Finger-nose-finger on left 8 times

(9) Open and close right hand 10 times

(10) Open and close left hand 10 times

(11) Alternatively pronate and supinate right hand 10 times

(12) Alternatively pronate and supinate left hand 10 times

(13) Tap right foot 10 times

(14) Tap left foot 10 times

(15) Jaw at rest for 5 seconds

(16) Mouth open for 5 seconds

(17) Sustained phonation: first 'AAA' for 10 seconds, then 'EEE'

(18) Head while patient is seated for 10 seconds

(19) The examiner will test the passive tone of each arm and leg and comment on this.

(20) Drawing 2 Archimedes spirals with each hand (subject should make at least 6 full circular motions)

While subject is standing:

(21) Hands hanging at sides for 10 seconds; assess legs too

(22) Walking 20 feet and turning

(23) Tandem gait for 10 steps

Assessment Scale

Criteria for definite ET (all 5 must be true)

1. On examination, a +2 postural tremor of at least 1 arm (a head tremor may also be present, but is not sufficient for the diagnosis).
2. On examination, there must be
    a. A +2 kinetic tremor during at least 4 tasks or
    b. a +2 kinetic tremor on 1 task and a +3 kinetic tremor on a second task; tasks include pouring water, using a spoon to drink water, drinking water, finger-to-nose, and drawing a spiral.
3. If on examination, the tremor is present in the dominant hand, then by report, it must interfere with at least 1 activity of daily living (eating, drinking, writing, or using the hands). If on examination, the tremor is not present in the dominant hand, then this criterion is irrelevant.
4. Medications, alcohol, parkinsonism, dystonia, other basal ganglionic disorders, and hyperthyroidism are not potential etiologic factors.
5. Not psychogenic (bizarre features, inconsistent in character, changing, subject is distractable, or other psychiatric features on examination.

Criteria for probable ET (1 and 3 to 5 must be true; also, either 2a or 2b must be true)

1. On examination, a +2 postural tremor of arms may or may not be present.

2. (a) Same as 2 above (see definite ET).
   (b) Head tremor is present on examination.
3. Tremor in dominant hand may or may not interfere with at least 1 daily activity.
4. Medications, hyperthyroidism, dystonia, or alcohol are not potential etiologic factors.
5. Not psychogenic.

Criteria for possible ET

1. On examination, a +2 kinetic tremor must be present on 3 tasks.
2. No other stipulations.

0-+3 Tremor ratings

0, No visible tremor.

+1, Low amplitude, barely perceivable tremor, or intermittent tremor.

+2, Tremor is of moderate amplitude (1 to 2 cm) and usually present. It is clearly oscillatory.

+3, Large amplitude (>2 cm), violent, jerky tremor resulting in difficulty completing the task due to spilling or inability to hold a pen to paper.

15.1.5 UPDRS (Unified Parkinson's Disease Rating Scale) Part III—Motor Examination

PART III: MOTOR EXAMINATION

MDS-UPDRS Part III [Goetz et al. 2008] will be used to assess any presence of motor symptoms of parkinsonism.

https://www.movementdisorders.org/MDS/Education/Rating-Scales.htm

15.1.6 DSM-5 Diagnostic Criteria for Major Neurocognitive Disorder [Hugo and Ganguli 2014]

Major Neurocognitive Disorders as Diagnosed in DSM-5

Diagnostic Criteria	Major Neurocognitive Disorder	
A	Significant cognitive decline in one or more cognitive domains, based on:	
	1.	Concern about significant decline, expressed by individual or reliable informant, or observed by clinician.
	2.	Substantial impairment, documented by objective cognitive assessment.
B	Interference with independence in everyday activities.	
C	Not exclusively during delirium.	
D	Not better explained by another mental disorder.	
E	Specify one or more etiologic subtypes, "due to" • Alzheimer's disease • Cerebrovascular disease (vascular neurocognitive disorder) • Frontotemporal lobar degeneration (frontotemporal neurocognitive disorder) • Dementia with Lewy bodies (neurocognitive disorder with Lewy Bodies) • Parkinson's disease • Huntington's disease • Traumatic brain injury • HIV infection • Prion disease • Another medical condition • Multiple aetiologies	

From[Hugo and Ganguli 2014]. Adapted from: American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association; 2013.

15.1.7 H & Y (Modified Hoehn and Yahr) staging

Table 3 Modified Hoehn and Yahr Staging

Stage 0:	No signs of disease
Stage 1:	Unilateral disease
Stage 1.5:	Unilateral plus axial involvement
Stage 2:	Bilateral disease, without impairment of balance
Stage 2.5:	Mild bilateral disease, with recovery on pull test
Stage 3:	Mild to moderate bilateral disease, some postural instability; physically independent
Stage 4:	Severe disability; still able to walk or stand unassisted.
Stage 5:	Wheelchair bound or bedridden unless aided.

15.2 Radiation dosimetry data

[^{123}I] has a physical half-life of 13.2 hours. As it decays, it emits gamma radiation with predominant energy of 159 keV and x-rays of 27 keV.

The estimated absorbed radiation doses to an average adult subject (70 kg) from IV injection of ioflupane [^{123}I] is listed below. The values are calculated assuming urinary bladder emptying at 4.8-hour intervals and appropriate thyroid blocking ([^{123}I] is a known Auger electron emitter). Frequent bladder emptying should be encouraged after dosing to minimise radiation exposure. Estimated absorbed radiation dose is shown in Table 4.

Table 4 Estimated Absorbed Radiation Doses to an Average Adult Patient

Target Organ	**Absorbed radiation dose µGy/MBq**
Adrenals	17.0
Bone surface	15.0
Brain	16.0
Breast	7.3
Gallbladder wall	44.0
Gastrointestinal tract	
Stomach wall	12.0
Small intestine wall	26.0
Colon wall	59.0
(Upper large intestine wall	57.0)
(Lower large intestine wall	62.0)
Heart wall	32.0
Kidneys	13.0
Liver	85.0
Lungs	42.0
Muscles	8.9
Oesophagus	9.4
Ovaries	18.0
Pancreas	17.0
Red marrow	9.3
Salivary glands	41.0
Skin	5.2
Spleen	26.0
Testes	6.3
Thymus	9.4
Thyroid	6.7
Urinary bladder wall	35.0
Uterus	14.0
Remaining organs	10.0
Effective Dose (µSv/MBq)	**25.0**

Ref.: Publication 128 of the Annals of ICRP (Radiation dose to Patients from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances, 2015)

The effective dose (E) resulting from administration of 185 MBq of DaTSCAN™ injection is 4.63 mSv (per 70 kg individual). The above data are valid in normal pharmacokinetic

behaviour. When renal or hepatic function is impaired, the effective dose and the radiation dose delivered to organs might be increased.

16 CLINICAL PROTOCOL AMENDMENT SUMMARIES

16.1 Amendment A01

16.1.1 Reasons for Amendment

The China Center for Drug Evaluation requested that GE Healthcare evaluate the Study GE-001-024 protocol according to the ICH E5 requirement. As a result, changes have been incorporated to provide better characterisation of DaTSCAN™ in the Chinese population and improve clarity of study procedures. Some procedures have been moved between the baseline and screening visits to ensure data required to make a clinical diagnosis will be available at the baseline visit. Protocol wording has been updated using the current GE Healthcare template.

16.1.2 Summary of Key Changes

The following key changes have been made throughout the protocol:

- Medical director details updated.
- Diagnostic criteria for PD updated to MDS Clinical Diagnostic Criteria for Parkinson's Disease following adoption in the China national guidelines and on the advice of the co-ordinating investigator. This reflects current medical practice in China and provides better scientific value to the study.
- Removed requirement for ECG assessment.
- Clarified that the DaTSCAN™ product will be supplied in a 5-mL vial.
- Laboratory testing moved from baseline to screening to allow sufficient time for processing of samples.
- Recruitment period corrected.
- Subject numbering system clarified.
- AE reporting updated in line with current standards.
- Clarification that AEs are to be recorded from time of informed consent.
- Text referring to paper CRFs deleted; electronic CRFs will be used.

16.2 Amendment A02

16.2.1 Reasons for Amendment

The Amendment is to provide further explanation and clarification to certain items in the protocol, to avoid potential ambiguity of interpretation, and ensure consistence of conduct between sites. Meanwhile, some wordings are revised according to idiomatic expression.

16.2.2 Summary of Key Changes

The following key changes have been made throughout the protocol:

- The GE Healthcare UK address and Medical Director details were updated.
- Prevalence and incidence of Parkinson's disease cited in this protocol were updated.
- Thyroid blocking treatment was updated to add clarification on timing of administration for before and/or after injection, the example was removed, and how to handle sourcing was updated.
- The final follow-up visit timing was changed from 48 (+48) hours to 72 (±24) hours.
- DSM-5 criteria were updated for use in inclusion/exclusion criteria. The term "dementia" was changed to "major neurocognitive disorder".
- Added Mini-Mental State Examination total score <24 requirement in the exclusion criteria.
- Changed classifying images "typical or atypical of PD" to "typical or atypical of SDD".
- Updated when prior medication needs to be collected.

16.3 Amendment A03

16.3.1 Reasons for Amendment

The main purpose of the Amendment is to update the timing of recruitment, overall study duration, and study visits.

16.3.2 Summary of Key Changes

The following key changes have been made throughout the protocol:

- The screening and baseline visits are to be performed within 28 days prior to the imaging visit.
- The follow-up visit changed from 72 (±24) hours to 3 (±1) days.
- Clarified the timing for performing injection site monitoring.
- Changed the number of centres from approximately 8 to approximately 10.
- Updated the recruitment period from approximately 9 months to approximately 18 months.
- Updated the overall study duration from approximately 10 months to approximately 18 months from First Patient First Visit to Last Patient Last Visit.
- Removed funduscopy.
- Updated the Medical Director on the title page.

SIGNATURE PAGE

Date / Name	Justification / Role
Signed By: [redacted] Date of signature: 25-Nov-2020 14:32:03 GMT+0000	Justification: Approved Role: Head of Clinical Development
Signed By: [redacted] Date of signature: 25-Nov-2020 15:28:18 GMT+0000	Justification: Approved Role: Head of Biometrics
Signed By: [redacted] Date of signature: 25-Nov-2020 15:42:28 GMT+0000	Justification: Approved Role: Head of Imaging Technology